CONCISE COMMUNICATION

Virus Load and Risk of Heterosexual Transmission of Human Immunodeficiency Virus and Hepatitis C Virus by Men with Hemophilia

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A high human immunodeficiency virus (HIV) load may increase the probability of HIV transmission by sexual contact, but the association of virus load of hepatitis C virus (HCV) with risk of HCV transmission is uncertain. HIV and HCV virus loads were examined in hemophilic men, as were risks of HIV and HCV transmission to their female partners in a hemophilia cohort in which most subjects are dually infected. A higher HIV load was associated with an increased risk of HIV transmission (odds ratio [OR], 1.31 per $\log_{10}$ increase in virus load). A higher HCV load was associated, although not significantly, with an increased risk of HCV transmission (OR, 1.42 per $\log_{10}$). HCV load was higher among dually infected men than in those infected with HCV alone ($P = .001$). However, much larger studies are needed to clearly show whether HIV/HCV coinfection significantly increases the risk of HCV transmission to female partners.

High levels of serum or plasma RNA virus load of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are each associated with increased risk of HIV and HCV transmission from mother to infant [1–3]. In men, HIV load is associated with risk of heterosexual transmission to their female partners [4–7], although the association of HCV load and risk of sexual transmission is uncertain. Most hemophilia patients who were treated with clotting factor concentrates during the late 1970s and early 1980s are dually infected with HIV and HCV and in general have a markedly elevated HCV load but no substantial change in HIV load [8]. The effect of an elevated HCV load among dually infected hemophilic men on the risk of HIV and HCV heterosexual transmission remains to be determined. To address this issue, we examined the association between HIV and HCV positivity among female partners of dually infected hemophilic men and the HIV and HCV loads in the men.

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Informed consent was obtained from all study participants. Study protocol followed the human experimentation guidelines of the US Department of Health and Human Services and the institutional review boards of the National Cancer Institute and participating treatment centers.

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Subjects and Methods

Study subjects. Subjects of this analysis were men with hemophilia or related clotting disorders and their female sex partners enrolled in the Multicenter Hemophilia Cohort Study (MHCS), a prospective study established in 1982 [9]. As of October 1998, 2179 index hemophilia cases from 17 treatment centers in the United States and Western Europe have been enrolled. In addition, 457 female sex partners, most married to patients, were separately recruited by the adult hemophilic men for HIV antibody testing, counseling, and study enrollment.

At initial enrollment and at each subsequent visit, peripheral blood samples were collected, separated, and frozen at −70°C in a central repository. Information on current use of blood products and HIV-related medical conditions was updated by systematic abstraction of the subject's medical records. Female partners also completed standardized self-administered questionnaires. Follow-up visits with additional questionnaires and blood-sample collection took place every 6–12 months. Of the 457 patient-partner pairs, 398 had complete HIV and HCV serology data. After we excluded 5 couples with reported history of injection drug use by female partners, the present analysis was composed of 393 couples.

Laboratory methods. HIV seropositivity was determined by repeated tests with a commercially licensed HIV-1 EIA. Positive results were confirmed by Western blot (Cambridge Biotech, Rockville, MD) or RIA [9]. HCV positivity was based on detection of serum or plasma antibodies by recombinant immunoblot assay (RIBA-II or -III; Chiron, Emeryville, CA), with reactivity to at least 2 of the 4 antigens. Less reactivity, with a single positive band or indeterminate bands, was considered HCV indeterminate. RIBA-indeterminate samples were considered HCV positive only if HCV RNA was detected, as described below.

Each hemophilic man's HIV and HCV load was determined from available samples drawn after September 1982, at least 1 year after HIV seroconversion and closest to the time that his partner's HIV

	Female partner data		Male patient data	
	HIV status	HCV status	Log_{10} HIV RNA	Log_{10} HCV RNA
1	+	-	5.0	6.3
2	+	-	5.5	6.2
3	+	-	5.5	6.9
4	+	-	5.1	7.9
5	+	+	5.2	7.1
6	+	-	5.7	7.7
7	+	-	4.0	6.8
8	+	-	4.2	5.4
9	+	-	3.4	7.0

□ Date of first sexual intercourse (truncated at 10 years)
♦ Date of HIV seroconversion in female partners
◊ Date of HIV load measurement
* Date of first sexual intercourse missing

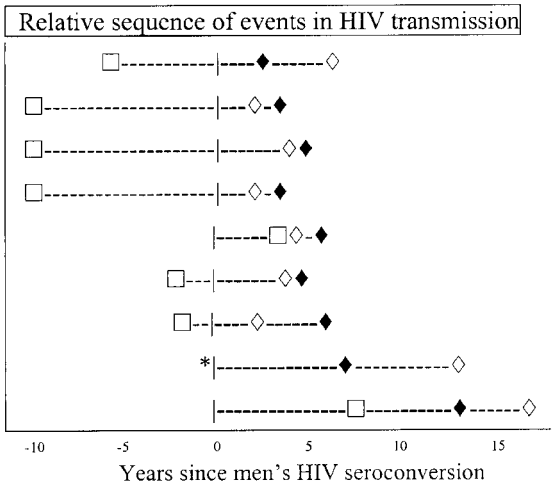

Figure 1. Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) serology, virus load, and relative sequence of events in HIV transmission among 9 male patient–female partner pairs with incident HIV infection among women in the Multicenter Hemophilia Cohort Study.

and HCV serostatus were determined. HIV RNA level was measured by Amplicor HIV Monitor assay (Roche, Branchburg, NJ). Quantification of HCV RNA was performed with the Quantiplex HCV 2.0 branched DNA assay (Chiron). Undetectable HIV or HCV loads among HIV- or HCV-positive men were set at midpoint between 0 and the lower limit of analytic sensitivity of the assay (2 and 5 on $\log_{10}$ scale for HIV and HCV, respectively).

Statistical analyses. HIV seroconversion dates in the hemophilic men were estimated as described elsewhere [10]. Comparisons of demographic characteristics across groups were made by the χ^2 statistic. HIV and HCV loads were $\log_{10}$ transformed and analyzed as continuous variables. Mean HIV loads among hemophilic men were compared by HCV infection status by Wilcoxon's rank sum test. Mean HCV loads were compared by HIV infection status in the same manner. Among HIV/HCV dually infected hemophilic men and their partners, the association of HIV positivity among women with the men's HIV load and the association of HCV positivity among women with the men's HCV load were estimated by the odds ratios (ORs) derived from logistic regression models [11]. Wald-type 95% confidence intervals (CIs) were calculated. Statistical significance was based on 2-sided tests. Exploratory analysis showed a linear, dose-effect relationship between HIV and HCV loads and risk of transmission. Therefore, we present the ORs per $\log_{10}$ increase in the results.

Results

The mean age at blood draw used for this analysis was 36 years for hemophilic men and 33 years for female partners. Of the 393 hemophilic men, 343 (87%) were infected with both HIV and HCV, 6 (2%) with HIV alone, and 42 (11%) with HCV alone; only 2 (1%) were infected with neither virus. Among female partners, 52 (13%) of 393 were HIV positive; 9 were seroconverters subsequent to their initial enrollment in the study. All 52 HIV-positive women were partners of HIV-positive men. Twenty-one (5%) of the 393 female partners were HCV positive at baseline. Only 1 (2%) of the 42 men with HCV infection alone transmitted HCV to his partner, compared with 20 (6%) of the 343 dually infected men ($P = .21$).

Mean HIV load was similar or slightly lower in the 343 dually infected men, compared with the 6 men infected only with HIV (4.6 vs. 5.3 $\log_{10}$ copies/mL, $P = .16$). In contrast, mean HCV load was significantly higher among men who were coinfected with HIV, compared with the 42 who were infected with HCV alone (6.6 vs. 6.2, $P = .001$). HIV load among men with HIV-positive partners was higher than among those with HIV-negative partners (4.9 vs. 4.5, $P = .03$). However, HCV load was not significantly higher among men with HCV-positive partners than among those with HCV-negative partners (6.7 vs. 6.6, $P = .52$).

Data for the 9 HIV-positive couples with incident HIV infection in the women are summarized in figure 1. Six of these 9 couples (case 1–4, 6, and 7) were sexually active before the man's HIV seroconversion. The mean interval between men's and women's seroconversion date was 67 months. Although all 9 women were partners of dually infected men, only 1 (case 5), who became sexually active after her partner's seroconversion, contracted both HIV and HCV.

Among 343 dually infected men, an increased risk of HIV transmission to female partners was associated with a higher HIV load (OR, 1.37 by a $\log_{10}$ increase in HIV RNA level; 95% CI, 1.01–1.86) and a lower CD4 cell count (OR, 1.15 per 100 decrease in CD4 cells; 95% CI, 1.00–1.31; table 1). Older age at HIV seroconversion was associated with a nonsignificantly

Table 1. The odds ratios (ORs) and 95% confidence intervals (CIs) for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission in female partners of 343 HIV/HCV-coinfected men in the Multicenter Hemophilia Cohort Study.

Parameter	HIV transmission, OR (95% CI)	HCV transmission, OR (95% CI)
Unadjusted		
HIV RNA (log_{10})	1.37 (1.01–1.86)	1.09 (0.67–1.78)
HCV RNA (log_{10})	1.03 (0.71–1.49)	1.22 (0.69–2.17)
CD4 cell count	1.15 (1.00–1.31)	0.97 (0.83–1.07)
CD8 cell count	1.05 (0.97–1.12)	1.03 (0.93–1.13)
Age at HIV seroconversion	0.84 (0.64–1.11)	0.82 (0.53–1.26)
Adjusted[a]		
HIV RNA (log_{10})	1.31 (0.94–1.84)	1.18 (0.70–1.99)
HCV RNA (log_{10})	1.13 (0.75–1.70)	1.42 (0.69–2.95)

NOTE. ORs are for HIV or HCV positive compared with negative. ORs for HIV and HCV RNA is per 10-fold increase in level; ORs for CD4 and CD8 cell counts are per 100 decrease in count; OR for age is per 10-year increase.

[a] Models mutually adjust for both HIV and HCV virus load, age at HIV seroconversion, and CD4 cell count.

lower risk of transmission (OR, 0.84; 95% CI, 0.64–1.11). Adjustment for HCV load, CD4 cell count, and age at HIV seroconversion slightly attenuated the association between sexual transmission and HIV load (OR, 1.31 per log_{10}; 95% CI, 0.94–1.84).

Risk of HCV transmission to female partners was not significantly increased with a higher HCV load (OR, 1.22 by a log_{10} increase in HCV RNA level; 95% CI, 0.69–2.17; table 1). However, this association was enhanced with adjustment for HIV load, age, and CD4 cell count (OR, 1.42; 95% CI, 0.69–2.95). Of the 343 coinfected men, 180 (52%) had multiple HCV load measurements over time. By use of the average HCV load as a predictor, the risk of HCV transmission was similar (OR, 1.40; 95% CI, 0.63–3.12).

Discussion

The positive correlation of HIV load and the risk of heterosexual transmission has been examined in several series with small numbers of patients [4–7]. The present study found a significant difference in HIV load between transmitters and nontransmitters, confirming the association of a high virus load with increased risk of male-to-female transmission of HIV in a larger population study. This finding supports the hypothesis that recent HIV seroconverters, whose virus load typically is highest at and during the first few months after initial infection, may be more likely to transmit. In our series, most HIV infections occurred among married women who likely were exposed to the initial peak of their husband's viremia. However, as we noted in a few previous cases [12], female seroconversions also occurred 3–12 years after the index patient's seroconversion, suggesting that the chronic level of viremia affects the subsequent risk of transmission.

We found that a lower CD4 cell count in HIV carriers was associated with a higher risk of sexual transmission. The finding suggests that low CD4 cells may be a marker for high peak viremia during the first few months after infection and confirms earlier observations of a higher risk of heterosexual transmission among hemophilic men with advanced immune deficiency [13, 14]. Although older age at seroconversion was previously found to be associated with more-severe depletion of CD4 cells and progression to AIDS [9, 14], it was not a risk factor for sexual transmission in the present study. Our data are unlikely to be confounded by therapy, since all the 52 HIV transmissions to women occurred before January 1996, when highly active antiretroviral therapy became available. However, the observed associations may have been confounded by changes in sexual activities owing to counseling and symptoms of HIV disease. Unfortunately, we could not examine the longitudinal sexual and clinical data with confidence, because the majority of the HIV-positive women had prevalent HIV infections that could not be accurately dated.

Thomas et al. [15] reported a 3.7-fold increase in risk of HCV transmission among female partners of HCV-infected men, compared with the partners of HCV-negative men. In the present study, we found that all HCV-positive women were partners of HCV-positive men and that the risk of HCV transmission was elevated by 42% with a log_{10} increase in HCV load. However, this association was not significant, perhaps because the event rate was relatively low. A lack of significant association of HCV load with risk of sexual transmission contrasts with the reported association of HCV load with risk of mother-infant transmission [3]. Possible explanations for this discrepancy include the relative resistance of the female genital tract against HCV infection, lower HCV RNA levels in semen than in serum, and confounding by sexual activities. Other cofactors required for sexual transmission of HCV remain unknown.

HCV load was in general much higher than HIV load within the same person, but fewer women were infected with HCV than with HIV. A lack of statistical significance between HCV load and risk of sexual transmission may be due in large part to our inability to measure HCV load near the time of transmission to the partner. Although our HCV-load measurement in the men may not be representative of their partners' relevant exposure, increases and fluctuations of HCV load over time [8] are unlikely to have biased our finding, since the association was unchanged when the mean HCV load over time was used as a predictor.

As would be expected from our previous report [8], we found a 3-fold increase in HCV load with HIV/HCV coinfection (6.6 vs. 6.2 on log_{10} scale). Thus, in the present analysis, a positive association of HCV load with the risk of sexual transmission, albeit not significant, raises the possibility that coinfection in men may increase the risk of HCV transmission to women partners to a small degree. Because only 6 men were infected with HIV but not with HCV, the effect of coinfection on HIV load could not be well studied. Moreover, the range of HCV load, with or without HIV, is broad. The association of a high

virus load with a higher risk of HIV and HCV transmission also may have been underestimated, if a high load is inversely correlated with "well being" of the men and thus with the frequency of sexual contact.

In summary, we found that, although HIV is associated with an increase in HCV load, it is unlikely to fuel an epidemic of sexually transmitted HCV. Much larger studies with detailed questionnaire data and multiple, frequently collected samples would clarify the effect of HIV and AIDS on the rate and modes of HCV transmission.

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